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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,121	01/03/2001	Shinji Kawai	146.1358	9941

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BIERMAN MUSERLIAN AND LUCAS
600 THIRD AVENUE
NEW YORK, NY 10016

EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	12

DATE MAILED: 04/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,121	KAWAI ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/9/01; 1/3/01; 2/21/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *5,11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-10* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-12 are pending.

Applicant's election with traverse of Group I, (Claims 1-4 and 6-10), drawn to a monomer protein comprising an amino sequence of SEQ ID NO: 2 filed 2/21/02, is acknowledged. The traversal is on the grounds that this is a 371 of the PCT application and it is deemed that the unity of invention found by the PCT has all the claims examined together. However, this is not found persuasive because Amatatayakul-Chantler *et al* (of record, Mol. Endo 8(3): 325-332, 1994; PTO 1449) teach a monomer protein such as Activin A, belonging to the TGFβ superfamily, comprising an amino acid sequence (See Fig 7, page 329, in particular) of which cysteine (residue 80) related to a dimmer formation of the protein has been replaced with another amino acid such as Alanine (See entire document, page 329, column 2, in particular). Since Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have single general inventive concept and lack unity of invention. Further, a prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement is still deemed proper and is therefore made FINAL.

2. Claims 5-9 and 11-12 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 1-4 and 6-10, drawn to a monomer protein comprising an amino sequence of SEQ ID NO: 2 for preventing and treating disease affecting bone and/or cartilage are being acted upon in this Office Action.

4. Applicant should amend the first line of the specification to reflect the relationship between the instant application and PCT/IB99/00866 filed May 14, 1999 as stated on the oath.

5. Claim 4 is objected because of the typographical error "SEQ ID NO.: 2"; it should have been "SEQ ID NO: 2".

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3 and 6-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a monomer protein comprising an amino acid sequence of SEQ ID NO: 2 wherein the amino acid sequence belonging to TGFβ superfamily of which cysteine at position 83 related to a dimmer formation of the protein has been replaced with alanine for induce differentiation of osteoblast and increases alkaline phosphatase activity *in vitro*, does not reasonably provide enablement for (1) *any* monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid, (2) the said monomer protein wherein another amino acid is an amino acid selected from the group consisting serine, threonine, alanine and valine, (3) the said monomer protein wherein another amino acid is alanine, (4) *any* agent comprising *any* monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid, containing an effective amount of the monomer protein for preventing and treating *any* disease affecting bone and/or cartilage, (5) the said agent for preventing and treating *any* disease affecting bone and/or cartilage wherein the disease is osteoporosis, (6) the said agent for preventing and treating *any* disease affecting bone and/or cartilage wherein the disease is osteoarthritis or arthrosteitis, (7) the said agent for preventing and treating *any* disease affecting bone and/or cartilage wherein the disease is bone fracture and (8) the said agent for preventing and treating *any* disease affecting bone and/or cartilage wherein the disease is a lack of root of teeth and a tooth socket. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one monomer protein comprising an amino acid sequence of SEQ ID NO: 2 that belongs to the TGFβ superfamily, having an amino acid substitution of cysteine for alanine at position 83 of SEQ ID NO: 2 wherein the monomer protein induces differentiation of osteoblast and increases alkaline phosphatase activity in vitro (See page 5, lines 10-15, pages 12-13).

Other than the specific monomer protein mentioned above, the specification does not teach how to make and use *any* monomer protein and *any* agent mentioned above for preventing and treating *any* disease affecting bone and/or cartilage. There is insufficient guidance and working examples of *any* "monomer protein comprising *any* amino acid sequence" that belongs to TGFβ superfamily having cysteine replaced with *any* other amino acid because there is no structure (the specific amino acids that comprises the amino acid sequence) and function of *any* amino acid sequence. Second, there is insufficient guidance as to which cysteine within said monomer protein mentioned above can be substitute and whether the resulting protein after substitution would maintain both structure and function as the unmodified monomer protein. Third, the term "comprising" is open-ended. It expands the undisclosed monomer protein comprising an undisclosed amino acid sequence to include additional amino acid at either end. Finally, Other than the specific monomer protein comprising SEQ ID NO: 2 mentioned above for induces differentiation of osteoblast and increases alkaline phosphatase activity in vitro, there is not even one in vivo working example using *any* monomer protein or agent mentioned above for treating any bone disease affecting bone and/or cartilage.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Mason *et al* teach amino acid substitution of *any* cysteine residues (there were 9 of them in total) of a monomer protein such as activin A comprising an amino acid sequence that belongs to the TGF-β superfamily from cysteine to alanine fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular) or loss biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) or loss of receptor binding activity (See Receptor Binding Activities of

activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach that the equivalent in TGFβ1 in which the cysteine residue corresponding to residue 77 when changed to a serine residue, the resulting secreted monomer has no bioactivity (See page 330, column 1, first paragraph, in particular). Given the indefinite number of undisclosed monomer protein comprising just *any* amino acid sequence and the lack of guidance as to which cysteine residue within said undisclosed amino acid sequence of the monomer protein can be substitute, it is unpredictable which undisclosed monomer protein comprising just any amino acid sequence that belongs to the TGFβ superfamily, after modification, would be useful for preventing and treating any disease that affecting bone and/or cartilage such as osteoporosis, osteoarthritis, arthrosteitis, bone fracture, and disease where a lack of root of teeth and tooth socket. Since the monomer protein is not enabled, it follows that protein wherein another amino acid has been replaced with another amino acid such as the ones recited in claims 2 and 3 is not enabled. It also follows that *any* agent comprising said monomer protein for preventing and treating a disease affecting bone and/or cartilage such as the ones recited in claims 7-10 are not enabled.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

8. Claims 1-3 and 6-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid, (2) the said monomer protein wherein another amino acid is an amino acid selected from the group consisting serine, threonine, alanine and valine, (3) the said monomer protein wherein another amino acid is alanine, (4) *any* agent comprising *any* monomer protein comprising *any* amino acid sequence belonging to TGFβ superfamily of which cysteine related to a dimmer formation of the protein has been replaced with *any* other amino acid, containing an effective amount of the monomer protein for preventing and treating *any* disease affecting bone and/or cartilage, (5) the said agent for preventing and treating *any* disease affecting bone and/or cartilage wherein the

disease is osteoporosis, (6) the said agent for preventing and treating *any* disease affecting bone and/or cartilage wherein the disease is osteoarthritis or arthrosteitis, (7) the said agent for preventing and treating *any* disease affecting bone and/or cartilage wherein the disease is bone fracture and (8) the said agent for preventing and treating *any* disease affecting bone and/or cartilage wherein the disease is a lack of root of teeth and a tooth socket.

The specification discloses only one monomer protein comprising an amino acid sequence of SEQ ID NO: 2 that belongs to the TGFβ superfamily, having an amino acid substitution of cysteine for alanine at position 83 of SEQ ID NO: 2 wherein the monomer protein induces differentiation of osteoblast and increases alkaline phosphatase activity *in vitro* (See page 5, lines 10-15, pages 12-13).

Other than the specific monomer protein comprising SEQ ID NO: 2 having a cysteine residue at position 83 replaced with alanine mentioned above for induces differentiation of osteoblast and increases alkaline phosphatase activity *in vitro*, there is insufficient written description about the structure associated with function of *any* monomer protein and *any* agent comprising said monomer protein mentioned above. Further, applicant discloses only one monomer protein comprising amino acid sequence of SEQ ID NO: 2 having only one amino acid substitution from cysteine to alanine corresponding to position 83 of SEQ ID NO: 2, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-3 and 6-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Mason *et al* (Molecular Endocrinology 8(3): 325-332, 1994; PTO 1449).

Mason *et al* teach a monomer protein such as activin A comprising an amino acid sequence that belongs to the TGF-β superfamily of which cysteine at position 80 related to a dimmer formation of the protein has been replaced with another amino acid such as alanine or serine (see page 327, column 1, in particular). Claims 6-10 are included in this rejection because the agent comprising the same monomer protein; an agent is the same agent irrespective of it's intended use. Thus, the reference teachings anticipate the claimed invention.

11. Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
April 8, 2002

Christina Chan
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640